probability distribution and parameter values for the incubation period were used.[16] During the early stages of the epidemic the relationship between variability in sexual activity, the proportion of individuals who are seropositive, and the number of AIDS cases is important. It is clear from fig 1 and the table that the cumulative number of AIDS cases beyond a given year depends not only on the distributed incubation period but also on the numbers of seropositive people at the time when transmission ceases. It is sometimes assumed that net mortality will be greatest if all those infected eventually develop AIDS and die. This is not necessarily true.[6] If infected people who do not proceed to AIDS have a similar life expectancy to uninfected people but remain infectious for life, then they may contribute more to net transmission than those who die of AIDS.[7]

A primary aim of model development is to aid in the identification of the types of quantitative data that are required to make reliable predictions. Our analyses identify studies of infectiousness and of sexual activity as being areas of particular importance. There is an obvious need to trace and monitor the sexual partners of HIV-infected patients, as well as to acquire quantitative data on viral abundance in the blood, secretions, and excretions of HIV-infected people throughout the duration of infection (which may be lifelong). Quantitative data on patterns of sexual activity are also difficult to acquire. Surveys based on interviews or questionnaires (perhaps carried out by professional market research organisations) need to collect numerical information on both the number of new sexual partners of each sex per person in samples stratified by age and sex over various specific intervals and the duration of each sexual partnership. Mean levels of activity are not sufficient—it is vital to acquire detailed data on variability in activity. In the UK it would seem particularly important to initiate the collection of such data immediately so that precise quantitative measurements are available to monitor the impact of the current publicity and educational campaign on AIDS. For effective assessment such data should have been collected before the campaign was introduced.

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Therapeutics

HIGH-DOSE VERSUS LOW-DOSE INTRAVENOUS IMMUNOGLOBULIN IN HYPOGAMMAGLOBULINAEMIA AND CHRONIC LUNG DISEASE

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Summary In a randomised cross-over study 12 patients with antibody deficiency and chronic lung disease received monthly infusions of either 0·6 g/kg or 0·2 g/kg intravenous immunoglobulin for six months, and were then switched to the alternative dose for a further six months. Although the incidence of infections did not differ greatly in the high-dose and low-dose phases, the frequency of acute infection was substantially reduced in those periods when serum IgG was 500 mg/dl or more. Pulmonary function worsened on the low-dose regimen and improved on the high-dose regimen.

INTRODUCTION

INTRAMUSCULAR injections of pooled human immune serum globulin (IgG) can reduce infections in patients with antibody deficiency,[1,2] and additional benefits have come from the introduction of modified IgG preparations for intravenous use (IVISG):[3,4] these can be given rapidly in larger amounts, without the pain and proteolytic degradation that occur at the intramuscular injection site.

As a prophylactic regimen to reduce severe infections in patients with antibody deficiency Gitlin and Janeway[2,5] selected a standard intramuscular dose of 0·1 g/kg monthly, and Ammann et al[6] have shown that in hypogammaglobulinaemia the same dose of IVISG is equipotent in preventing infections. However, in patients with chronic sinopulmonary disease and hypogammaglobulinaemia 0·1 g/kg seems insufficient: bigger doses further reduce the rate of major infections and improve lung disease.[4] We report here a comparison of 0·2 g/kg and 0·6 g/kg IVISG in 12 patients with antibody deficiency and chronic sinopulmonary disease.

PATIENTS AND METHODS

Patients

10 patients were classified as having common variable immunodeficiency and 2 as having X-linked agammaglobulinaemia. 4 were females and 8 were males. Median age at the onset of the study was 24 years (range 7–50). Patients were selected only if they had chronic pulmonary disease as established by clinical signs and symptoms of chronic cough and frequent acute exacerbations of pneumonia, radiographic abnormalities of the chest, and pulmonary function tests at least 25% below predicted values. In 4, chronic lung disease had developed despite regular intramuscular replacement therapy and in 5 there had been gradual worsening of lung disease over 1–7 years of conventional IgG replacement. The other 3, who presented with chronic lung disease, had not previously been treated.

Protocol and Evaluation

The study was conducted from June, 1985, until June, 1986, and the IVISG preparation was 'Sandoglobulin' (Sandoz, Montreal). For the first six months the patients were allocated randomly to

receive either 0·2 g/kg or 0·6 g/kg IVISG monthly and for the second six months they were switched to the alternative dose. They were monitored carefully for side-effects, including alterations in heart rate, respiratory rate, blood pressure, and temperature.

3 patients had repeated reactions to IVISG, but these could be prevented by administration of hydrocortisone before the infusion (as described previously[4,7]). Mild reactions consisting of headache and pyrexia were controlled by adjustment of the infusion rate.

Each treatment visit included a physical examination, a review of the health status from patients' diaries kept daily, and an interview. Sputum for culture was obtained at every visit as well as blood for cell counts and immunoglobulin measurements. Chest and sinus radiographs and spirometric recordings[8] were made before the start of the investigation and every three months thereafter. Spirometry technicians and radiologists were not told about the protocol.

RESULTS

A total of 144 IVISG infusions were administered to the 12 patients during the study. In patients receiving 0·6 g/kg, serum IgG (measured before each infusion) gradually increased to 500 mg/dl or more within two to four months (fig 1A). When the dose was reduced to 0·2 g/kg serum IgG fell rapidly in 4/6 patients and was below 500 mg/dl in all 6 after the third or the fourth month. The 6 patients who were initially assigned to 0·2 g/kg in no instance achieved a serum IgG of 500 mg/dl or more (fig 1B).

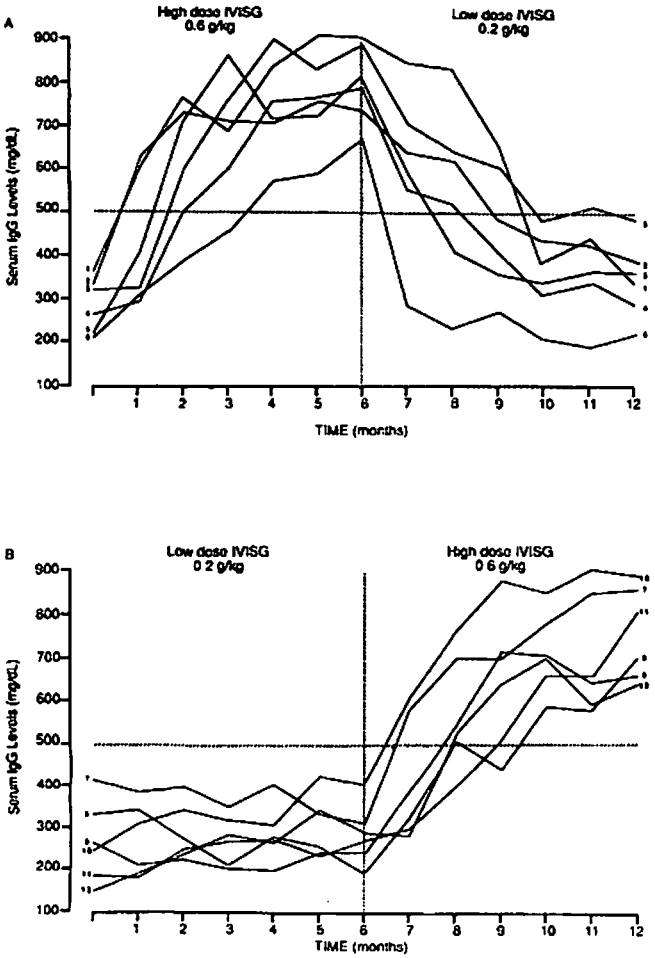

Fig 1—Serum IgG concentrations.

A, initial high dose; B, initial low dose.

INFECTIONS IN PATIENTS WITH ANTIBODY DEFICIENCY AND CHRONIC SINOPULMONARY DISEASE

	Serum IgG < 500 mg/dl		Serum IgG ≥ 500 mg/dl	
—	No of episodes	No of patients	No of episodes	No of patients
Minor infections				
Upper respiratory tract infections	23	12	10	7
Otitis	4	2	1	1
Urethritis	1	1	–	–
Skin infections	3	2	1	1
Total	31		12	
Major infections				
Acute exacerbation of lung disease/pneumonia	11	8	3	3
Sinusitis	4	2	–	–
Arthritis	1	1	–	–
Total	16		3	

Infections

Acute infections were divided into two categories. The first category included mild infections such as upper respiratory disease which did not lead to hospital admission. Overall, 43 such episodes were recorded in the 12 patients' diaries—24 episodes during the low-dose phase and 19 during the high-dose phase. When these episodes of acute infection were analysed according to serum IgG, a notable difference in frequency of acute infections emerged. In periods when serum IgG was less than 500 mg/dl the number of acute infections was 31; but in periods when serum IgG was 500 mg/dl or more there were only 12. (The total periods for which serum IgG was above and below 500 mg/dl were nearly identical.) In the second category, patients with severe acute infections necessitating hospital admission, the differences were more striking: in periods when serum IgG was below 500 mg/dl 16 major infections were recorded including pneumonia, sinusitis, and arthritis; whereas in periods when IgG was over 500 mg/dl only 3 admissions were required, all for pneumonia (table). Mycoplasmas were the major pathogenic organism identified in patients with either major or minor infections.[9]

Lung Indices

At the beginning of the study, all 12 patients had radiographic evidence of chronic chest disease, including peribronchial thickening, interstitial fibrosis, lobar atelectasis, and bronchiectasis. None of the patients improved radiographically during the low-dose therapy period and 3 of 12 patients showed chest deterioration. In 4 of 12 patients there was radiographic improvement by the end of the high-dose IVISG period.

8 patients had radiographic evidence of sinusitis: in 5 there was improvement by the end of the high-dose IVISG period whereas no change was observed during the low-dose phase. All patients had a chronic cough on entry to the study and in 11 of 12 this was less severe after high-dose IVISG.

In all 6 patients switched from high-dose to low-dose IVISG, forced vital capacity (FVC) and forced expiratory volume in the first second (FEV_1) deteriorated. In contrast, in the 6 patients switched from low-dose to high-dose IVISG there was a consistent improvement. In 10 of 12 patients the improvement or deterioration was greater than

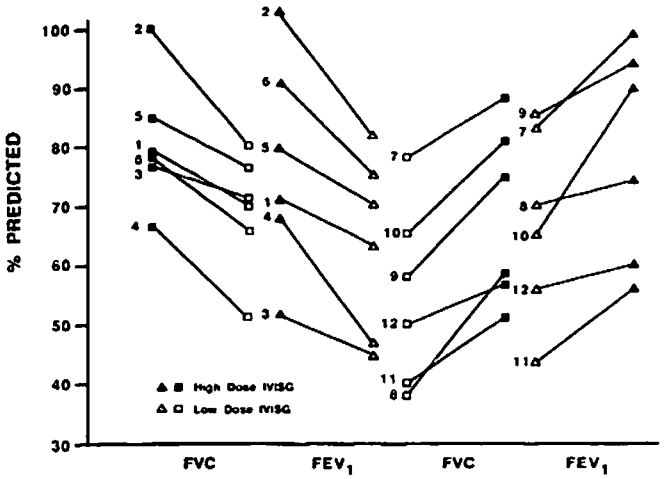

Fig 2—Pulmonary function tests.

Spirometry was done at the end of each six month period. FVC and FEV_1 are shown as percent predicted.

10% (range 10–50%). When analysed by the F-test under cross-over design[10] the means of FVC and FEV_1 values were significantly higher during the high-dose phase than during the low-dose phase ($p < 0.001$).

DISCUSSION

The incidence of infections during the low-dose and high-dose phases was very similar, probably because serum IgG changed only slowly after an increase or decrease in IVISG dosage. We found that the incidence of infection was related to periods in which the serum IgG was 500 mg/dl or more. The most striking differences associated with the two regimens were in pulmonary function tests. Spirometric indices had improved in all patients at the end of the high-dose treatment period, while the results at the end of the low-dose IVISG replacement were significantly worse. In this short-term study no major radiographic changes were observed, but improvement in chest radiographs has been seen in patients treated with high-dose IVISG for up to eighteen months.[4] We conclude that, in patients with chronic sinopulmonary disease, doses of IVISG that give a serum IgG of 500 mg/dl provide better protection against infection than the more conventional dose of 0·2 g/kg.

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Occasional Survey

INSULIN AND ATHEROMA—AN UPDATE

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IN 1969 Vallance-Owen and I hypothesised that high levels of circulating insulin are related to the pathogenesis of atherosclerosis.[1] The information that has accumulated since then is largely supportive. In this paper I review the hypothesis in the light of existing information. For brevity, only one reference is given for each statement even though in many instances confirmatory evidence has been published.

INSULIN AND CARDIOVASCULAR DISEASE

In 1969 the evidence linking hyperinsulinaemia with cardiovascular disease came from six studies of insulin levels in subjects who had recovered from myocardial infarction. Subsequent work has confirmed the relation between insulin and cardiovascular disease and has yielded details of its nature. We now know that insulin concentrations are raised not only in myocardial infarction but also in coronary artery atherosclerosis identified by angiography,[2] cerebrovascular disease,[3] and peripheral vascular disease[4]—ie, hyperinsulinaemia is associated with the disease of the artery rather than with myocardial ischaemia. In general the high insulin concentrations have been associated with oral glucose intake while fasting insulin levels,[5] and insulin responses to intravenous glucose,[6] tolbutamide,[6] or arginine,[7] have been normal; these observations point to an enhanced gastrointestinal stimulus to insulin release, the nature of which remains unknown.

There is now evidence that high insulin concentrations predispose to the development of cardiovascular disease. For example, white South Africans or Edinburgh men, with their high prevalences of cardiovascular disease, have more pronounced insulin responses to oral glucose than Bantus[8] or aged-matched Stockholm men[9] with their lower prevalences. The best evidence comes from prospective epidemiological studies of ischaemic heart disease conducted in Helsinki,[10] Paris,[11] and Busselton, Western Australia.[12] In each there was a significant association between insulin concentration and the development of ischaemic heart disease and this was independent of other risk factors including lipids, blood pressure, and smoking. The relation between insulin and cardiovascular disease was not linear or dose-dependent but more in the nature of a threshold effect.

DIABETES

Although diabetes is often regarded as a disease of insulin deficiency, insulin concentrations are commonly above normal in non-insulin-dependent diabetics who are obese[13] as well as in patients using insulin.[14] High insulin concentrations may also be found in patients with early or mild diabetes,[15] and in populations at increased risk of becoming diabetic.[16]

The relation between insulin levels and large vessel disease in diabetic subjects has received little attention, despite incidental findings in early studies pointing to a link.[17,18] Groups in Munich[19] and Kuopio[20] have shown that diabetic patients with macrovascular disease have higher fasting plasma C-peptide concentrations (indicating greater endogenous insulin secretion), higher daily insulin doses, and higher fasting free insulin or 2-hour post-glucose serum insulin concentrations than diabetics without vascular disease. In the only prospective study, diabetic patients in Oxford who had normal electrocardiograms (ECGs) on presentation and abnormal ECGs five years later had higher fasting insulin concentrations both before and after the abnormality developed than those whose ECGs were normal on both occasions.[21]

Because of the high frequency of cardiovascular disease in diabetes and the potential implications for management, further prospective studies are urgently needed.